The Expanding Universe of Neurotrophic Factors: Therapeutic Potential in Aging and Age-Associated Disorders

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Abstract: Multiple molecular, cellular, structural and functional changes occur in the brain during aging. Neural cells may respond to these changes adaptively by employing multiple mechanisms in order to maintain the integrity of nerve cell circuits and to facilitate responses to environmental demands. Otherwise, they may succumb to neurodegenerative cascades that result in disorders such as Alzheimer's and Parkinson's diseases. An important role in this balancement is played by neurotrophic factors, which are central to many aspects of nervous system function since they regulate the development, maintenance and survival of neurons and neuron-supporting cells such as glia and oligodendrocytes. A vast amount of evidence indicates that alterations in levels of neurotrophic factors or their receptors can lead to neuronal death and contribute to aging as well as to the pathogenesis of diseases of abnormal trophic support (such as neurodegenerative diseases and depression) and diseases of abnormal excitability (such as epilepsy and central pain sensitization). Cellular and molecular mechanisms by which neurotrophic factors may influence cell survival and excitability are also critically examined to provide novel concepts and targets for the treatment of psysiological changes bearing detrimental functional alterations and of different diseases affecting the central nervous system during aging.

Keywords: Aging, neurodegeneration, age-associated disorders, neurotrophic factors, mimetic peptides, growth factor synthesis inducer.

BRAIN CHANGES DURING AGING

It is well established that healthy aging is accompanied by multiple changes in many brain regions and functional decline in a number of cognitive domains [1]. Normal changes in brain physiology occur over time and can gradually result in slower information processing and alterations in memory function. In particular, most prominent among age-related brain changes are slowing of cognitive processing speed, diminished ability to acquire and recall new information, increased difficulty ignoring distractions, focusing attention and recalling to mind appropriate words. These age-related changes are thought to be the result of ongoing physiological processes that would begin in youth, but, depending on factors such as genetic background and lifestyle, generally become evident and start to affect cognition in middle age and beyond.

In spite of a large body of descriptive work on the cellular, structural and functional changes occuring during brain aging, a general view is lacking and the molecular mechanisms underlying loss of neuronal plasticity, perceived as the key element of brain aging, are to date largely unknown [2]. The described age-related changes of the human brain include a decline in total brain volume and weight, especially in the frontal lobes and hippocampus, regions essential for learning and memory, associated with cortical thinning, gyral atrophy and white-matter degradation [3]. These changes may be due to nerve cell loss or cell shrinkage and, among the various brain areas, hippocampus seems to be particularly vulnerable [4]. However, evidence suggest that neuronal loss observed in some brain regions could be compensated by expansion of dendritic arbors and increased synaptogenesis in the remaining neurons [5]. Moreover, neuronal changes may also occur, with a decline in neurotransmitters and receptors, a decrease in the number of synapses and a deterioration of axons and dendrites, which contribute to the impairment of neuronal function [6].

Changes in the cellular structure of the brain and the functions of its neuronal circuits are controlled by a complex array of inter-cellular signalling molecules and intracellular signal transduction pathways. Several such cellular signal transduction systems are altered during brain aging. Among neurotransmitter systems, dopaminergic signalling appears to be consistently altered during aging with a progressive decrease in signalling via the D2 subtype of receptor [7-8]. Furthermore, altered serotonin (5-HT) signalling has been recently considered as another contributing factor to aging [8-9]. Examples of widely used intracellular signalling mechanisms affected by aging include protein phosphorylation (alterations in kinases and phosphatases) [10], cellular calcium homeostasis [11-12], and gene transcription [13-14]. Within this context, the middle age and aged groups show an upregulation of cortical genes and pathways related to oxidative damage and inflammation, and downregulation of genes associated with DNA repair and synaptic function, particularly for vesicular transport and neurotransmission [14,15-17]. In addition to signalling pathways, cellular systems that regulate protein folding and degradation are altered in brain cells during aging [18]. These kinds of alterations that occur during normal aging may set the stage for neurodegenerative cascades that result in disorders such as Alzheimer's and Parkinson's diseases, that in turn may be triggered by particular genetic predispositions or environmental factors, while other age-related changes may represent adaptive protective responses to the aging process.

In regard to the molecular and cellular mechanisms that determine whether brain aging occurs successfully or manifests dysfunction or disease, the major classes of signalling molecules important in brain aging include neurotrophic factors, neuro-transmitters, cytokines and steroids.

In particular, an important role in balancing protective/ neurodegenerative processes is played by neurotrophic factors, which are central to many aspects of nervous system function since they regulate the development, maintenance and survival of neurons and neuron-supporting cells such as glia and oligodendrocytes.

NEUROTROPHIC FACTORS

Neurotrophic factors (NTFs) are diffusible peptides secreted from neurons and neuron-supporting cells. NTFs belong to several superfamilies of structurally and functionally related molecules: 1) neurotrophins, including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and NT-4; 2) transforming growth factor (TGF)-β superfamily, which includes among others the glial-cell-line-derived neurotrophic factor

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Table 1. Classification of the Neurotrophic Factors Superfamilies in Humans

Neurotrophic superfamily factors	Family/Member	Sub-member
NGF superfamily	NGF	
	BDNF	
	NT-3	
	NT-4	
TGFβ superfamily	GDNF family	GDNF
		Neurturin
		Artemin
		Persephin
	TGFβ family	TGFβ1
		TGFβ2
		TGFβ3
	Bone morphogenetic protein family	Bone Morphogenetic Protein 1
		Bone Morphogenetic Protein 2
		Bone Morphogenetic Protein 3
		Bone Morphogenetic Protein 4
		Bone Morphogenetic Protein 5
		Bone Morphogenetic Protein 6
		Bone Morphogenetic Protein 71
		Bone Morphogenetic Protein 8a
		Bone Morphogenetic Protein 8b
		Bone Morphogenetic Protein 10
		Bone Morphogenetic Protein 15
Neurokine superfamily	CNTF	
	Interleukin-6	
	Interleukin-11	
	Leukemia inhibitory factor	
	Oncostatin M	
	Cardiotrophin-1	
	Granulocyte colony-stimulating factor	
Non-neuronal factors	IGF-1	
	Acidic fibroblast growth factor	
	Basic fibroblast growth factor	
	Epidermal growth factor	

(GDNF); 3) neurokine superfamily and 4) non-neuronal factors (for a more detailed list, see Table **1**).

NTFs have been shown to promote the survival of specific populations of brain neurons under experimental conditions relevant to brain aging and neurodegenerative disorders [19]. NTFs exert their effects on the development and function of neurons by binding to cell surface receptors possessing intrinsic tyrosine kinase activity, in turn activating downstream kinases including the phosphatidylinositol-3-kinase, protein kinase Cγ, and the mitogen-activated protein kinase, as well as several small G-proteins, inclu-

ding Rap-1 and the Cdc-42-Rac-Rho family [20]. As a consequence, one or more transcription factors including AP1, NF-κB and FOXO are activated and ultimately the expression of genes that encode proteins involved in regulating neuronal survival, differentiation and plasticity is induced.

One or more of these various growth factors and mechanisms may fail during development, neuronal repair and aging causing disease including, but not limited to, neurodegenerative illnesses. Indeed, their abnormal trophic support for selective neuronal populations has been proposed to contribute to the pathogenesis of depression, neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS) and also aging [21-29]; in parallel, alterations in levels of NTFs or their receptors have been correlated to diseases of abnormal excitability such as epilepsy and central pain sensitization [29-30].

This review is focused on some NTFs for which data of recent human clinical studies and trials are available unraveling their therapeutic potential in a variety of diseases states and aging. In particular, we included NGF, BDNF, GDNF, insulin-like growth factor I (IGF-I) and ciliary neurotrophic factor (CNTF).

NEUROTROPHINS

As previously mentioned, neurotrophins include NGF, BDNF, NT-3 and NT-4. Neurotrophin receptors are typically present in the neurites (axons and dendrites) of growing neurons during development, and in pre and postsynaptic terminals of neurons in the mature nervous system. Neurotrophins exert their effects by interacting with two structurally unrelated receptors, the tyrosine receptor kinase (Trk) and p75, which differ for ligand specificity and signal transduction activities. Neurotrophins are synthesized as precursors with major dimension and then cleaved by furin and proconvertase to produce mature protein. In their active cleaved form, each neurotrophin selectively activates one of three types of Trk receptors. NGF binds the TrkA receptor, BDNF and NT-4 bind to TrkB, and NT-3 binds TrkC [31]. All four neurotrophins can bind to the low-affinity p75 neurotrophin receptor. Binding of neurotrophins to their Trk receptors causes signalling events which promote neuron survival, whereas activation of the p75 neurotrophin receptor pathway triggers apoptosis and cell death [32]. Proneurotrophins bind to the receptor sortilin (also known as the neurotensin-3 receptor) [33] and p75, which, like TrkA and p75, interact to form an high-affinity binding site [34], which appears to mediate the neurotoxic effects of proNGF [34] and also proBDNF [35]. Thus, the role of proneurotrophins and neurotrophins appears to be opposite: neurotrophins maintain survival and function to certain neuronal populations, whereas proneurotrophins trigger cell death through p75.

NERVE GROWTH FACTOR-NGF

NGF, the first member of neurotrophin family, supports neuronal survival during development and modulates neuronal functions throughout adulthood. The highest NGF protein levels have been observed in the hyppocampus, cortex and olfactory bulb, where most NGF-producing cells are neurons [36]. In central nervous system (CNS), aging and age-related cognitive impairments are known to correlate with the cellular atrophy of basal forebrain cholinergic neurons (BFCN). BFCN provide major projections to the cerebral cortex and the hippocampus and cortical cholinergic mechanisms are known to be directly involved in cognitive functions such as learning and memory [37]. NGF is synthesized by hippocampal and cortical neurons and is retrogradely transported to BFCN cell bodies [38-39]; it plays a key role in regulating survival and in maintaining the biochemical and morphological phenotype of adult BFCN [40-41]. BFCN in turn express both TrkA and p75 NGF receptors [38] and respond to administration of exogenous NGF by increasing phenotypic cholinergic markers [42]. Therefore, within the central cholinergic system, changes in NGF have been associated with age-dependent cognitive function and cognitive impairment following brain damage [43]. When a loss of NGF support occurs, cholinergic neurons show cell shrinkage, reduction in fiber density and down-regulation of transmitter-associated enzymes (cholinoacetyl-transferase-ChAT and acetylcholinesterase-AChE), thus resulting in a decrease of cholinergic transmission [44]. Investigations in the past decades have shown that administration of NGF to the BFCN *in vitro* leads to an increased survival and to an up-regulation of ChAT activity [45]. Furthermore, NGF infusion in aged rats ameliorates significantly deficits in spatial recent memory and to a minor extent also those concerning reference memory [40]; in addition, chronic intraventricular infusion of NGF has been demonstrated to restore long-term potentiation (LTP) deficits in old cognitively-impaired rats to levels equivalent to the control group [46]. Furthermore, the ability of NGF to prevent degeneration of BFCN has also been demonstrated in non-human primate brain [47].

A severe cholinergic degeneration is also typical of AD, where a reduction of ChAT and AChE activity and BFCN size and number was observed [48-49]. This connection has provided a strong argument to link NGF and AD. Support for the role of NGF in AD was provided by knockout mice lacking both NGF and TrkA which showed large reductions in ChAT immunoreactivity in the basal forebrain and loss of cholinesterase activity in both the hippocampus and cortex [50]. A loss of the NGF receptor TrkA was found in the basal forebrain [51] and in the cortex [52] of AD brains. According to the hypothesis that NGF deprivation is one of the factors involved in the etiology of sporadic forms of AD, a mouse model (AD11 anti-NGF mice) had been developed, based on the expression of transgenic antibodies neutralizing NGF. The model is characterized by a progressive neurodegenerative phenotype defined by the deposition of amyloid peptide, by intracellular neurofibrillary tangles and by a marked cholinergic depletion [53]. In addition, spatial memory and neocortical LTP are impaired in AD11 mice at an age corresponding to early neurodegenerative stage.

Since changes of NGF concentrations have been reported in the course of different experimental disease models, there is evidence that endogenous NGF levels follow a distinctive temporal pattern [54-55]. Postmortem studies point to a lack of NGF action in early stages of AD [56], i.e. at the onset of neurodegeneration. In the majority of the neurodegenerative diseases, this reduction is followed by a raise of NGF concentration, which could be read as neuroprotective effort of counterregulation that should lead to adequate NGF levels in endangered NGF-dependent neurons. This hypothesis is supported by the fact that increased NGF concentrations were found in the hippocampus, cortical and subcortical regions of post-mortem AD brains [57], together with decreased NGF immunoreactivity in the basal forebrain [58]. These observations further suggest that there is a dysfunction in retrograde transport of NGF from the target tissues (hippocampus and neocortical areas) to the BFCN cell bodies. In fact, axonal transport processes are essential in delivering the proper NTF signalling, mainly concerning survival effects. Whereas local effects induced by neurotrophins, such as the modulation of synapses, do not require the retrograde axonal transport of neurotrophins to the cell bodies, for survival effects neurotrophins must have the ability to transduce a series of complex signalling events from the nerve terminal plasma membrane to the nucleus located in the cell bodies. Most neurodegenerative dementias are linked to failures in axonal transport, i.e. defects in long-range neurotrophin signalling from distal axons to cell bodies. This led to the prediction that, more generally, failed axonal transport of NGF signals might provide a common link among reduction of NGF trophic support, cholinergic dysfunction and neurodegeneration [59].

Interestingly, a novel way in which neurotrophins could contribute to neurodegeneration has been suggested. As previously reported, in addition to their effects on normal neuron function, NTFs and receptors have been proposed to contribute to the deleterious effects of old age and degenerative disease in the CNS [60]. Recent studies highlight how the precursor of neurotrophins may be either neurotoxic [61] or significantly less neurotrophic than its mature form [62]. Within this context, Al-Shawi et al. found age-associated increases in proNGF (the predominant form of NGF in the human and rodent brain) protein expression, as well as in sortilin protein, in the targets of neurons vulnerable to age-related neurodegeneration. These proNGF levels correlate positively with vulnerability to age-related neuronal cell death and proNGF-induced neurotoxicity appears to be mediated by sortilin [63]. However, understanding whether proNGF has adaptive roles in development and how its *in vitro* trophic effects are mediated needs further elucidation.

Altered levels of NGF have also been reported in other neurodegenerative disorders, such as PD (characterized by selective loss of nigral dopaminergic neurons) and ALS (characterized by a degeneration of the lower motor neurons in brain stem and spinal cord and the upper motor neurons in the cerebral cortex) as well as in diseases of abnormal excitability, such as epilepsy. Investigations in the past decades showed that, in substantia nigra and striatum of patients with PD, a small decrease in staining density for NGF has been observed [64]. Moreover, two studies on ALS found that mRNA and protein levels of NGF were increased [65-66]. Moreover, the levels of NGF mRNA were found increased in response to kindling as well as epileptic seizures in animal models of epilepsy [67]. Despite these observations, to date no human clinical trials have been performed with NGF in these diseases.

NGF GENE-THERAPY

As opposed to PD and ALS, due to the efficacy in improving the survival and the maintenance of cholinergic neurons, the concept of therapeutic administration of human recombinant NGF in AD patients shows a strong rationale, being further validated by recent and ongoing clinical trials with a gene-therapy approach. Within this context, NGF gene therapy by Ceregene (CERE-110, the NGF gene in an adeno-associated virus [AAV]-based vector) has been tried in a phase I clinical study on eight patients with early-stage AD. This therapy, involving NGF-grafted autologous fibroblasts that are implanted in the basal forebrain, showed a slower progression of dementia, some cognitive improvement and sprouting of axons on the site of injection [68] (see Table **2**).

Another study on the effect of intraventricular injections of NGF to AD patients showed some beneficial effects but also adverse side effects, such as weight loss and the induction of pain [69]. However, to date, because of poor pharmacokinetic profile and difficulties in the delivery of protein into the brain, the widespread clinical application of gene or cell-therapy strategies for the delivery of NGF to AD patients seems unpractical, and it would be more advantageous to have non-invasive methods, that should also limit the adverse effects of NGF in activating nociceptive responses [68,70-71].

NGF RECEPTOR MIMETICS

The development of small molecule neurotrophin receptor mimetics, or of NGF agonists in general, retaining the biological activity of the natural protein, was undertaken [72-73]. Until now the production of such drugs has required the mass screening of large libraries of synthetic chemicals. The approaches aiming to isolate small molecule mimetics are based on structural studies, starting from the tertiary structure of NGF, and comprise various types of compounds, most of them based on the search for an NGF mimetic able to induce an activation of the receptors, TrkA and/or p75 [73] (see text and Table **2**). The recent findings of the increasing role of proNGF in neurodegeneration of the CNS through p75 receptor raise the possibility of targeting the p75 with small molecules, able to inhibit proNGF-induced cell death. One strategy is based on synthetic peptide mimetics of NGF loop 1, that could prevent cell death, since they seem to activate p75 and the downstream pathways involving NFκB and PI3K [72]. Furthermore, dimeric peptidomimetics based on the loop 4 on NGF, termed P92, were shown to act as partial NGF agonists, by interacting with TrkA receptor and activating ERK and AKT signalling [74]. Recently, a new NGF-mimetic peptide, termed L1L4, was identified, by combining loop 1 and 4 in the same molecule [75]. This peptide was able to induce TrkA phosphorylation and differentiation of PC12 cells, thus showing a good NGF-like activity *in vitro*, but showed the capability to reduce pain in an animal model of injury, which is inconsistent with the actions of NGF in neuropathic pain [76]; therefore, these data indicate that this compound is not yet ready for a clinical application. A different class of small molecules with NGF agonistic activity relies on the finding that the TrkA receptors can also be activated in the absence of neurotrophins, through transactivation by G-protein coupled receptor ligands (Table **2**) [77-80]. To date, however, a better understanding of properties *in vivo* of these NGF agonists is required in order to evaluate their potential for the treatment of neurodegeneration. Moreover, it is worth to underline that some of these small molecule ligands have a mixed agonistic and antagonistic profile, which makes it difficult to predict their behavior *in vivo*.

NGF SYNTHESIS INDUCERS

Other strategies to increase the NGF neurotrophic support to the brain are based on the use of drug-releasing NGF biodegradable microspheres implanted into brain [81]. Furthermore, NGF synthesis inducers, proNGF/NGF processing modulators and proNGF antagonists have also been investigated (see text and Table **3**) [82-87].

It is interesting to notice that many of these pharmacological agents, recognized as modulators of NGF expression, have proven useful in the symptomatic treatment of neurodegenerative diseases. As an example, the AChE inhibitor Huperzine A, currently in Phase II clinical trial, increases NGF mRNA and protein levels after transient cerebral ischemia [82]. Xaliproden, a combined NGF potentiator and 5-HT_{1A} receptor agonist, showed NGF effects *in vitro* and *in vivo* and delayed the progression of the motor neuron degeneration [83]. Ifenprodil, originally developed as an effective cerebral vasodilator, and then reported to act as an NR_{2B}-selective NMDA receptor antagonist, has been shown to exhibit marked cytoprotective activities in animal models for focal ischemia and PD, strongly enhancing the production, besides other growth factors, of NGF [87]. Another possible approach consists in the identification of NGF processing modulators, able to interfere with the activity of proteases known to cleave proNGF, in order to act on the proNGF levels in disease states. However, due to the wide distribution of the proteases and their targets, a potential therapeutic intervention should be accurately designed in order to target the specific cellular populations affected in the disease [21,25]. Finally, in the framework of the investigation towards the use of the neurotrophin system in the therapeutic intervention for AD, another possibility could be based on the use of proNGF antagonists. In particular, the potential use of neurotensin as an antagonist for proNGF resides on the findings that the peptide competes with proNGF for the binding to sortilin [34]. However, the effects mediated by the binding of neurotensin to sortilin are presently not fully understood [88].

BRAIN-DERIVED NEUROTROPHIC FACTOR-BDNF

BDNF, the second member of the neurotrophin family, is a small dimeric protein, which is abundantly expressed in the adult

Table 2. Classification of NTFs Gene-Therapy or Receptor Mimetics Currently in Research and Development, on the Basis of their Mode of Action and Indication. The Table has been Built on the Basis of the Search on the Site ClinicalTrial.gov (Consulted 26 February 2009) and/or the Site(s) of the Producers

Neurotrophic factor	Molecole	Profile of compound versus growth factor	Indication	Pharmacological action	Clinical phase	Reference
NGF	NGF	Adeno-virus delivered NGF	AD		Phase I	68
	P92	NGF agonistic activity	AD	Direct binding of TrkA receptor	Preclinical	74
	LIL4	NGF agonistic activity	AD	Direct binding of TrkA receptor	Preclinical	75-76
	Neotrofin (AIT-082)	NGF agonistic activity	AD, memory disorders	Analog of hypoxanthine	Phase IB	77
	Adenosine	NGF agonistic activity	AD, neurodegeneration, pain	Transactivation by G-protein coupled receptors	Preclinical	78-79
	N-PEP-12	NGF peptidomimetic	AD, memory disorders	Derivative of cerebrolysin	Phase II	80
BDNF	BDNF	Adeno-virus delivered BDNF	PD, ALS		Preclinical	125
GDNF	GDNF	Recombinant-methionyl human GDNF (Liatermin)	PD		Phase I	ClinicalTrial. gov
	GDNF	Recombinant-methionyl human GDNF & Synchro Med Infusion System (continuously administered using chronically implanted catheters and pumps)	Progressive Supranuclear Palsy		Phase II	ClinicalTrial. gov
	XIB4035	GDNF receptor mimetic	PD	Direct binding of GFRα1 receptor	Prelinical	176
Neurturin	Neurturin	Adeno-Associated Virus Serotype 2 [AAV2]-Neurturin	PD		Phase II	185, 186 ClinicalTrial. gov
Artemin	Neublastin	Recombinant human artemin	Neuropathic pain	Ligand for the Ret receptor	Preclinical	187
CNTF	CNTF	Implants of encapsulated human NT-501 cells releasing CNTF	Retinitis Pigmentosa		Phase I	204
	CNTF	Implants of encapsulated human NTC-201 cells releasing CNTF	Visual Acuity Impairment, Atrophic Macular Degeneration		Phase II	204
IGF-1	Mecasermin (myotrophin)	Recombinant insulin-like growth factor-1	AD ALS	Direct binding of IGF-1R receptor	Phase IIA Phase III	224, 225 231
	Capromorelin (CP-424,391)	Pyrazolinone-piperidine dipeptide growth hormone secretagogue	Aging	Agonist of the GH secretagogue receptor	Phase II	228
	IGF-1	Adeno-virus-delivered IGF-1	ALS		Preclinical	232

Table 3. Classification of Various Drugs having another Recognized Mechanism of Action as NTFs Synthesis Inducers. The Drugs Listed are Approved for Use or Currently in Research and Development and are Classified on the Basis of their mode of Action and Indication. The Table has been Built on the Basis of Available data Sheets of the Drugs Approved for Use and on the Search on the Site ClinicalTrial.gov (Consulted 26 February 2009) and/or the Site(s) of the Producers

Neurotrophic factor	Molecule	Profile of compound versus growth factor	Indication	Pharmacological action	Clinical phase (*)	Reference
NGF	Huperzine A	NGF synthesis inducer	AD	AChE inhibitor	Phase II	81
	Xaliproden (SR57746A)	NGF synthesis inducer	AD, ALS	NGF potentiator and 5-HT_{1A} receptor agonist	Phase III	83
	Selegiline	NGF synthesis inducer	PD	Monoamine oxidase-inhibitor	Approved	84
	Rasagiline	NGF synthesis inducer	PD	Monoamine oxidase-inhibitor	Approved	85
	CGP 36742	NGF synthesis inducer	Neurodegeneration	$GABA_B$ receptor antagonist	Preclinical	86
	CGP 56433A	NGF synthesis inducer	Neurodegeneration	$GABA_B$ receptor antagonist	Preclinical	86
	CGP 56999A	NGF synthesis inducer	Neurodegeneration	$GABA_B$ receptor antagonist	Preclinical	86
	Ifenprodil	NGF synthesis inducer	PD	NR_{2B}-selective NMDA receptor antagonist	Preclinical	87
	Imipramine	NGF synthesis inducer	Depression	Tricyclic antidepressant	Approved	114
BDNF	Ifenprodil	BDNF synthesis inducer	PD	NR_{2B}-selective NMDA receptor antagonist	Preclinical	87
	Imipramine	BDNF synthesis inducer	Depression	Tricyclic antidepressant	Approved	114
	Fluoxetine	BDNF synthesis inducer	Depression	Selective Serotonin Reuptake Inhibitor	Approved	114
	Tranylcypromine	BDNF synthesis inducer	Depression	Irreversible monoamine oxidase Inhibitor	Approved	114
	Venlafaxine	BDNF synthesis inducer	Depression	Serotonin and Noradrenaline Reuptake Inhibitor	Approved	114
	Memantine	BDNF synthesis inducer	Moderate-severe AD	NMDA receptor antagonist	Approved	133
	L-DOPA	BDNF synthesis inducer	PD	Dopamine precursor	Approved	134
	Pramipexole	BDNF synthesis inducer	PD, Restless Legs Syndrome	D_3 receptor agonist	Approved	136
	Ropinirole	BDNF synthesis inducer	PD	D_3 receptor agonist	Approved	136
	Apomorphine	BDNF synthesis inducer	PD	D_1/D_2 receptor agonist	Approved	137
	Selegiline	BDNF synthesis inducer	PD Major Depression	Monoamine oxidase-inhibitor	Approved Phase III	135 138
	Rasagiline	BDNF synthesis inducer	PD	Monoamine oxidase-inhibitor	Approved	85
	SGS742	BDNF synthesis inducer	AD	$GABA_B$ receptor antagonist	Phase II	139
	Ladostigil (TV3326)	BDNF synthesis inducer	PD, AD	Monoamine oxidase- and cholinesterase inhibitor	Preclinical	140, 141
	Ampalex (CX516)	BDNF synthesis inducer	AD/dementia	AMPA receptor potentiator	Phase II	ClinicalTrial.gov
	Biarylpropylsulfonamides (LY392098, LY404187, LY503430)	BDNF synthesis inducer	PD, depression, CNS disorders	AMPA receptor potentiator	Preclinical	142

(Table 3) Contd….

Neurotrophic factor	Molecule	Profile of compound versus growth factor	Indication	Pharmacological action	Clinical phase (*)	Reference
	Org24448	BDNF synthesis inducer	Depression	AMPA receptor potentiator	Phase II	143
	Tacrolimus (FK506)	BDNF synthesis inducer	PD	Immunosuppressive immunophilin ligand	Preclinical	144, 145
	GPI-1046	BDNF synthesis inducer	PD	Non-immunosuppressive immunophilin ligand	Preclinical	144, 145
	Tripchlorolide (TW397)	BDNF synthesis inducer	PD	Chinese herbal compound (extract of Tripterygium wilfordii Hook F)	Preclinical	146
GDNF	PYM50028	GDNF synthesis inducer	PD AD	Plant-derived compound obtained from a traditional Asian "tonic"	Preclinical Phase II	177 ClinicalTrial.gov
	Tacrolimus (FK506)	GDNF synthesis inducer	PD	Immunosuppressive immunophilin ligand	Preclinical	145
	GPI-1046	GDNF synthesis inducer	PD	Non-immunosuppressive immunophilin ligand	Preclinical	145
	Apomorphine	GDNF synthesis inducer	PD	D_1/D_2 receptor agonist	Approved	137
	Pramipexole	GDNF synthesis inducer	PD, Restless Legs Syndrome	D_3 receptor agonist	Approved	136
	Ropinirole	GDNF synthesis inducer	PD	D_3 receptor agonist	Approved	136
	Cabergoline	GDNF synthesis inducer	PD	D_2/weak D_1 agonist	Approved	177
	Selegiline	GDNF synthesis inducer	PD Major Depression	Monoamine oxidase-inhibitor	Approved Phase III	135 138
	Rasagiline	GDNF synthesis inducer	PD	Monoamine oxidase-inhibitor	Approved	85
	L-DOPA	GDNF synthesis inducer	PD	Dopamine precursor	Approved	178
	Amantadine	GDNF synthesis inducer	PD HD		Approved Phase II	179
	Memantine	GDNF synthesis inducer	Moderate-severe AD	NMDA receptor antagonist	Approved	179
	Riluzole	GDNF synthesis inducer	ALS	Na^+ channel blocker	Approved	180
	Amitriptyline	GDNF synthesis inducer	Depression, panic, social anxiety, generalized anxiety and obsessive-compulsive disorder	Noradrenaline and serotonin reuptake inhibitor	Approved	181
	Clomipramine,	GDNF synthesis inducer	Depression, panic, social anxiety, generalized anxiety and obsessive-compulsive disorder	Noradrenaline and serotonin reuptake inhibitor	Approved	181
	Mianserine	GDNF synthesis inducer	Depression	adrenergic alpha2-autoreceptors and alpha2-heteroreceptors antagonist, 5-HT2 and 5-HT3 blocker	Approved	181

(Table 3) Contd….

Neurotrophic factor	Molecule	Profile of compound versus growth factor	Indication	Pharmacological action	Clinical phase (*)	Reference
	Fluoxetine	GDNF synthesis inducer	Depression, anxiety, obsessive-compulsive disorder	Selective Serotonin Reuptake Inhibitor	Approved	181
	Paroxetine	GDNF synthesis inducer	Depression, anxiety, obsessive-compulsive disorder	Selective Serotonin Reuptake Inhibitor	Approved	181

(*) Clinical phase refers to the indication for which the molecule is currently in use or in development.

mammalian brain. BDNF shares about 50% amino acid identity with NGF, NT-3 and NT-4 [89]. BDNF is abundantly expressed in the CNS, mainly in the hippocampal formation, cerebral cortex and amygdaloid complex [90]. Earlier efforts in NGF cellular biology showed that also BDNF is retrogradely transported by peripheral and CNS neurons; however, recent findings demonstrated that BDNF is also anterogradely transported in the CNS, a fact that has considerably expanded the concept of neuronal-derived trophic support [91]. BDNF expression increases until reaching a maximal level after birth [92] and then seems not to decline with age [93], thus suggesting essential roles for BDNF in the adult CNS. BDNF, through the interaction with its high-affinity receptor TrkB, is important for the survival and maintenance of different types of neurons and enhances neurogenesis. In particular, BDNF promotes the differentiation of neural progenitor cells into neurons and the survival of newly generated neurons [94]. In addition, BDNF is noteworthy for its role as a mediator of the effects of environmental factors on hippocampal neurogenesis. Levels of BDNF are increased in the hippocampus in response to exercise [95], dietary energy restriction [94] and cognitive stimulation [96], all of which stimulate neurogenesis. In the CNS, BDNF is also involved in synaptic plasticity, since its expression has been found increased in the hippocampus during learning-related events or after LTP induction [97-98]. In aged rats, conversely, both induction of BDNF by LTP and the associated signalling is decreased. However, the role of BDNF in the aging brain is discussed. There is evidence showing an increase in BDNF concentration in dentate gyrus from aged rats [99]. While, in other studies no changes in BDNF levels were found in rat hippocampus during the aging process, thus suggesting that rather alterations in BDNF receptors could occur during aging [100]. This speculation is reinforced by the past observations that BDNF administration did not counteract spatial learning impairments in aged rats [101].

In addition to its critical role in helping shape the vertebrate nervous system during development, BDNF is of particular therapeutic interest because of its neurotrophic actions on neuronal populations involved in several neurodegenerative diseases [102], including motor neurons, which degenerate in ALS [103], dopaminergic neurons of the substantia nigra, lost in PD, and BFCN involved in AD [104]. More recently, it has been demonstrated that BDNF probably plays a specific role in the etiology of HD [105].

With respect to AD, BDNF is well known to be a regulator of synaptic function and synaptic plasticity as well as of BFCN and therefore its possible implication in AD is well grounded. BDNF is able to promote survival of BFCN [106] and directly stimulate, in these neurons, the release of acetylcholine [107], thus suggesting that deficits of BDNF synthesis could partecipate in disrupting the cellular homeostasis resulting in AD. A decreased expression of BDNF and its receptor TrkB has been found in postmortem regions from AD patients, thus suggesting a potential role for compromised neurotrophic support in neuronal susceptibility to AD. In particular, a decreased transcript abundance of BDNF mRNA was found in hippocampus and entorhinal cortex in AD brains [57,108]. Interestingly, Murer *et al.* observed that neurons containing neurofibrillary tangles did not express BDNF, whereas neurons with no tangles expressed it, suggesting a possible protective role against neurofibrillary degeneration [109].

Other different lines of evidence point to a specific role for BDNF in the neuronal degeneration observed in PD. BDNF colocalizes with dopamine neurons in the substantia nigra, which are among the most prominent populations of neurons to degenerate in PD. In substantia nigra and striatum of patients with PD a small decrease in staining density for BDNF has been observed [110], underlining that reduced amount of this neurotrophin may be involved in the etiology and pathogenesis of PD. Interestingly, partial deletion of TrkB receptor induces a decreased number of neurons in the substantia nigra of old mice, together with a reduced expression of tyrosine hydroxylase and an increased formation of α-sinuclein deposits [111], thus suggesting that BDNF support is important for nigrostriatal dopaminergic neurons during senescence.

Alteration in BDNF expression have also been reported in ALS, where one study found that mRNA and protein levels of BDNF were increased [66]. Also TrkB mRNA was upregulated in spinal cords from ALS patients [112]. Within neurodegenerative disorders, a recent work implicated BDNF in HD as well [113]. Huntingtin, the protein mutated in HD, upregulated BDNF transcription, and loss of huntingtin-mediated BDNF transcription led to loss of trophic support to striatal neurons, which subsequently degenerated in the hallmark pathology of the disorder [113]. In addition, a reduction in the level of BDNF protein has been observed in the striatum and cortex of transgenic mice overexpressing mutant huntingtin. Furthermore, in patients with HD, BDNF levels were found decreased by 45% in cortical brain tissue [113].

Alterations in BDNF signalling may also be involved in mood disorders, such as depression, and in the mechanism of action of antidepressant drugs. A role for BDNF in the action of antidepressant treatments is supported by several lines of evidence. BDNF mRNA expression is decreased by stress in the hippocampus, whereas several antidepressant drugs are able to enhance it [114]. Compared with normal human subjects, levels of BDNF have been reported to be lower in postmortem brain tissue from depressed patients but higher in those taking antidepressants at the time of death [115]. Moreover, brain imaging studies have documented a reduction in hippocampal volume in depressed subjects, which can be attenuated by antidepressant treatment [116]. Interestingly, the implication of BDNF in mood disorders has been reinforced by a recent study of Pollak and coworkers [117]. They

recently suggested an animal model of a behavioral antidepressant, referred as learned safety, that shares some neuronal hallmarks of pharmacological antidepressants, as it increases the expression of BDNF in the hippocampus and also promotes the survival of newborn cells in the dentate gyrus of the hippocampus [117].

Alterations in BDNF levels have also been involved in the pathogenesis of diseases of abnormal excitability, such as epilepsy and central pain sensitization, which is an activity-dependent increase in excitability of dorsal horn neurons resulting in a clinically intractable condition termed "neuropathic pain" [118]. Recent *in vitro* and *in vivo* findings implicated BDNF in the cascade of electrophysiologic and behavioural changes underlying the epileptic state. BDNF mRNA and protein are markedly upregulated in the hippocampus by seizure activity in animal models [67,114] and infusion of anti-BDNF agents [118] or transgenic truncated TrkB-overexpression [119] inhibit epileptogenesis in animal models. Conversely, overexpression of BDNF in transgenic mice leads to spontaneous seizures [120] and intrahippocampal infusion of BDNF is sufficient to induce seizure activity *in vivo* [121]. Moreover, BDNF may play an important neuromodulatory role in pain transduction [122]. BDNF is synthesized by dorsal horn neurons and markedly upregulated in inflammatory injury to peripheral nerves [123]. Electrophysiological and behavioural data demonstrated that inhibition of BDNF signal transduction is able to inhibit central pain sensitization [124].

Altogheter these data suggest an exciting potential for therapies aimed at replacing BDNF or otherwise mimicking its actions in these disorders.

BDNF GENE-THERAPY

To date, a number of clinical trials investigated the therapeutic potential of BDNF, mainly in neurodegenerative disorders. With regard to PD, preclinical studies used AAV to deliver BDNF into brain; the injection into the substantia nigra was able to modulate locomotor activity without significantly affecting nigrostriatal dopaminergic survival [125] (see Table **2**). Furthermore, the use of polymers with fibroblasts genetically engineered to produce BDNF has been tested in AD models [126]. However, no human studies with BDNF have been performed in PD, as well as in AD and HD patients. To date, human clinical trials with BDNF have only been performed in ALS, with disappointing results, due to the small number of patients and the contrasting results [127-129].

BDNF RECEPTOR MIMETICS

The failure of clinical trials with recombinant BDNF is due to poor bioavailability, choice of an acceptable dosing regimen and difficulties in the delivery of protein into the brain; thus alternative ways to exploit BDNF actions for therapy are required. The development of small molecule BDNF peptidomimetic was and is currently undertaken [130-131]. Starting from the tertiary structure of BDNF, a tricyclic dimeric peptide was designed to mimic a cationic tripeptide sequence in loop 4 of BDNF that contributes to the binding of BDNF to the receptor p75. However, recombinant neurotrophin molecules acting through direct activation of the Trk receptors have shown disappointing results in many clinical trials [132]. It remains to be seen whether the currently available neurotrophin mimetics will result in drugs that effectively harness neurotrophin actions for therapeutic use.

BDNF SYNTHESIS INDUCERS

Other strategies to increase the BDNF neurotrophic support to the brain are based on the use of BDNF synthesis inducers. Drugs clinically used to treat AD (memantine) [133], PD (L-Dopa, selegiline, rasagiline, pramipexole, ropinirole, apomorphine) [85,134-137], depression [114,138] share the property to modulate BDNF levels in brain regions directly involved in the pathophysiology of the disease (see Table **3**). As previously mentioned, ifenprodil can modulate expression of different NTFs, among which BDNF, thus suggesting the indication as a potential agent for the treatment of neurodegenerative disorders such as AD, PD and HD [87]. Among the drugs that are currently being tested in clinical trials for AD, the compound SGS742 gained interest, since, in addition to be a $GABA_B$ receptor antagonist, is able to stimulate BDNF synthesis [139]. Furthermore, the bifunctional drug ladostigil has been demonstrated to combine neuroprotective and cognitive enhancing effects in models of AD and PD [140-141]. Moreover, AMPA receptor modulators might be used to treat cognitive dysfunctions, since they potentiate the glutamatergic synaptic transmission that contributes to cognitive functions. A number of structurally unique AMPA receptor potentiators has been shown to enhance BDNF expression *in vivo* and to modulate synaptic function [142-143]. Within this group of molecules, CX516 and Org24448 are currently in clinical development for a number of CNS disorders, including depression, PD and AD (see **Table 3**).

Modulation of Trk receptor signalling cascades has been suggested as another therapeutic potential. Interestingly, the Trk receptor pathway can be directly enhanced by immunophilin ligands, which mediate their neurotrophic activity via the FK506-binding proteins [144]. FK506 increased BDNF expression in mouse and human astrocyte cultures and striatal expression of BDNF and TrkB [145] putatively through binding to FKBP-52 with subsequent modulation of the Ras/Raf/MEK pathway. A similar effect was also observed in the presence of the non-immu-nosuppressive immunophilin ligand GPI-1046 [145]. Finally, closely related to FK506, the immunosoppressive chinese herbal compound Tripchlorolide protected dopaminergic neurons in a PD model and stimulated an increase in BDNF expression [146]. However, since all the mentioned pharmacological interventions have other direct effects on neuronal signalling, in addition to modulate BDNF, more studies are needed to establish the precise relevance of their BDNF modulating activity to their systemic effect.

GLIAL-CELL-DERIVED NEUROTROPHIC FACTOR FAMILY

GDNF family ligands are a group of polypeptides, structurally related to the TGFβ superfamily, which are produced by target cells and have been implicated in survival and differentiation of several neuronal subpopulations in the developing nervous system. GDNF represents the first-studied member of this family and is involved in the neuritic outgrowth and survival of dopaminergic neurons of the substantia nigra, BFCN, brainstem noradrenergic neurons and Purkinje cells both *in vitro* and *in vivo* [21,147-148]. Besides GDNF, this family also includes neurturin, persephin and artemin. Neurturin (NRTN) is expressed and supports the survival of nigrostriatal neurons during development and adulthood [148], whereas persephin is involved in survival of motor and midbrain dopaminergic neurons [149]. Artemin (ART) is poorly expressed in fetal and adult human brain, but is present in the basal ganglia and thalamus. This member has been implicated in the maintenance and survival of sensory and sympathetic peripheral neurons [150]. Each of these members exerts its actions by interacting with specific receptors, thus triggering intracellular signalling cascades. The action of these NTFs on neurons is similar to that of the neurotrophins but with distinct differences. A common receptor binds all growth factors in the subfamily and a specificity receptor exists able to distinguish factors within the subfamily. In particular, GDNF family receptors (GFR) comprise a receptor complex composed by the Ret proto-oncogene product and one of the four subtypes of glycosyl phosphatidylinositol (GPI)-anchored co-receptor GFRα (α1-α4). Each GDNF family member selectively activates one of four types of GFRα receptors thus leading to the activation of the Ret tyrosine kinase receptor. GDNF binds the GFRα1 receptor [151] and neurturin, persephin and artemin show a preference for GFRα2, GFRα3, GFRα4 respectively [21]. However, these binding specificities are not exclusive, since GDNF can bind

to GFRα2 and GFRα3, but with lower affinity, and then activate Ret [152].

GLIAL-CELL-DERIVED NEUROTROPHIC FACTOR-GDNF

GDNF supports the development of embryonic dopamine neurons and is particularly important for postnatal survival of mesencephalic dopamine neurons [147]. It is present in the striatum and despite, being named glial-derived growth factor, may reside abundantly in the striatal medium spiny neurons receiving dopaminergic input from the substantia nigra [153]. GDNF and its receptors are also widely expressed in hippocampus from early embryonic ages to adulthood [154]. Furthermore, GDNF has been found in the human peripheral nerve axons and in Schwann cells [155]. By analogy with the neurotrophins, GDNF is subjected to retrograde transport, being internalized by distal axons and transported to the cell bodies [156]. However, little or no information is available yet about the mechanisms of retrograde signalling used by GDNF family.

GDNF binds to GFRα-1 leading to the activation of the receptor tyrosine kinase Ret [151]. This activation initiates many of the same signal transduction pathways elicited by other tyrosine kinase receptors, including the mitogen-activated protein kinases Erk-1 and Erk-2 and the serine-threonine kinase Akt [157]. Through this signalling pathway, GDNF regulates the differentiation and survival of neurons by modulating the expression of antiapoptotic genes, such as Bcl-2, and others involved in neurotransmitter synthesis (such as tyrosine hydroxylase) [158-159]. In addition, a GDNF signalling independently of Ret has also been demonstrated. In the absence of Ret, GDNF has been shown to induce tyrosine phosphorylation of the MET receptor tyrosine kinase, as well as the activation of Fyn and FAK kinases [160-161], thus stimulating cell migration and neurite outgrowth. Noteworthy, several works demonstrated that GDNF contributes to synaptic transmission and can also play a role in learning and memory. GDNF increases the synaptic efficacy of dopaminergic neurons in culture by inducing new functional synaptic terminals [162]; recently a role for GDNF signalling in hippocampal synaptogenesis has been described [163].

A role for GDNF in aging is based on the observations that it is able to reverse some aspects of aging in monkey [164]. Besides cognitive deficits, it is known that aging is also associated with impaired motor function, including reductions in movement speed and coordination. This decline is likely due to decreased dopaminergic trasmission in the basal ganglia, a brain region important for coordinating movements. GDNF has been demonstrated to modulate dopamine function in association with motor function recovery in animal models of aging and PD. In aged rhesus monkeys, GDNF was able to increase the size and number of substantia nigra neurons and the density of dopaminergic nerve fibers in the putamen [164-165]. Furthermore, it also restored dopaminergic axons in the striatum and improved MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) induced-parkinsonian behavioral ratings [166]. Therefore, since its discovery in 1993, GDNF has been an attractive treatment option for PD due to its neurotrophic effects on dopaminergic neurons [167]. Moreover, the observations that GDNF is also a potent survival factor for spinal motoneurons also highlighted clinical implications for the treatment of ALS [168].

Concerning PD, current treatments provide only symptomatic relief and are unable to prevent the progressive death of neurons, besides to induce significant side effects. For these reasons, GDNF may represent an attractive therapeutic target for PD treatment. Many studies in animal models and some clinical trials in PD patients show that GDNF delivery can have trophic effects and restore motor function [169-170] (see Table **2**).

GDNF GENE-THERAPY

As previously reported, delivery of NTFs such as GDNF to the brain is problematic due to their inability to cross the blood-brain barrier, their brain diffusion and side-effects associated with binding to extra-target receptors. A possibility to overcome these limitations and at the same time to raise the concentration of therapeutic NTFs in a target tissue could be based on gene and cell-therapy approach, namely viral vectors or the implantation of cells programmed to secrete the NTF of interest [171-172]. Within this context, human neural progenitor cells engineered to secrete GDNF, implanted into the striatum of rats, increased dopamine neuron survival and fiber proliferation [173].

GDNF RECEPTOR MIMETICS

Another potential choice to generate trophic actions in the CNS is based on small molecules capable of crossing the blood-brain barrier and directly stimulating receptors or transduction mechanisms of NTFs [152] (see Table **2**). For example, a small nonpeptide quinol, XIB4035, can bind to GFRα1, thus inducing a conformational change responsible for GDNF receptor-Ret complex activation, and has been demonstrated to mimic neurotrophic effects of GDNF in Neuro-2A cells [174]. Furthermore, PYM-50028, a novel non-peptide NTF inducer, increased striatal GDNF and attenuated the loss of dopaminergic neurons from the substantia nigra in MPTP-lesioned mice [175]. In addition, based on the fact that the blood-brain barrier is more permeable to immunophilin ligands than to NTFs, immunophilins are considered another promising treatment for neurodegenerative diseases. Besides BDNF, as previously reported, tacrolimus and GPI-1046 strongly enhanced also GDNF content in the mouse substantia nigra, but not in the striatum, when administered subcutaneously for 7 days, which suggests that the immunophilin ligand-induced neurotrophic-like activity may be dependent on GDNF or BDNF expression [145].

GDNF SYNTHESIS INDUCERS

Finally, it is also interesting to underline that many drugs used in the symptomatic treatment of PD are recognized as modulators of GDNF expression, as well as of other neurotrophic factors (Table **3**). Since dopaminergic activity is able to promote GDNF expression (for a review see [176]) and the main characteristic of PD is the striatal dopamine deficit, drugs increasing dopaminergic transmission, such as dopamine receptor agonists (apomorphine, cabergoline, pramipexole and ropinirole) [136-137,177] or dopamine uptake and dopamine metabolism inhibitors (selegiline, rasagiline) [85, 135] have been demonstrated to induce GDNF expression in the nigrostriatal system (see Table **3**). In contrast to the effect of dopamine agonists on GDNF expression, the effect of the dopamine precursor L-DOPA on GDNF levels in the nigrostriatal system has not been extensively addressed. Only one study by Saavedra and coworkers demonstrated that L-DOPA can also induce GDNF up-regulation at the mRNA and protein levels in nigrostriatal system [178]. Finally, another drug used for the management of PD, the NMDA receptor antagonist amantadine, stimulated GDNF expression, which partially contributes to its neuroprotective properties observed in many *in vitro* and *in vivo* models [179].

Besides PD, also several drugs clinically used to treat AD (memantine) [179], ALS (riluzole) [180] and depression (amitriptyline, clomipramine, mianserine, fluoxetine and paroxetine) [181] share the property to modulate GDNF levels in brain regions directly involved in the pathophysiology of the disease (see Table **3**).

NEURTURIN AND ARTEMIN

Within the GDNF family, also NRTN and ART have gained in the last years particular attention. NRTN is a structural and

functional analog of GDNF that binds to GFRα2 receptors coupled to Ret [182]. NRTN has been shown to enhance survival of dopaminergic neurons both *in vitro* and in rodent and monkey models of PD [183-184]. In the latter studies, therapeutic administration of human recombinant NRTN into the striatum of the aged rhesus monkeys has been validated by recent and ongoing clinical trials with a gene-therapy approach. Within this context, NRTN gene therapy by Ceregene (CERE-120, an adeno-associated type 2 viral vector that encoded for human NRTN) is currently in phase II clinical trials [185] (see Table **2**). Preclinical studies suggested that intrastriatal CERE-120 injection could induce neurturin expression in the rat striatum for at least 1 year. Postmortem examination also revealed an increase in tyrosine hydroxylase immunoreactivity in the injected striatum [186].

ART has been shown to support the maintenance and survival of sensory and sympathetic peripheral neurons [150]. Recently, its potential application for the treatment of peripheral neuropathies has been proposed [187]. In fact, NsGene in Denmark and Biogen Idec in the United States are collaborating in the preclinical development of ART, termed neublastin, that has shown efficacy in animal models of neuropathic pain. Injections of the protein neublastin promoted the regeneration of damaged sensory nerve cells and produced virtually complete long-term restoration of sensory and motor function [187]. These studies suggest neublastin has potential for further development as a treatment for traumatic nerve injury [132].

NEUROKINE FAMILY

The neurokine family includes several members: CNTF, interleukin-6, interleukin-11, leukemia inhibitory factor (LIF), oncostatin M, cardiotrophin-1 and granulocyte colony-stimulating factor, as reported in Table **1**. All members are related to cytokines and show analogy concerning tertiary structure and signalling pathways through cell surface receptors, namely, leukemia-inhibitory factor receptor (LIFR) and gp130 [188-189]. Neurokines are involved in neuronal and glial differentiation and development, regulate both neuronal survival and phenotypic expression of neuropeptides and neurotransmitters and rescue neurons from axotomy-induced cell death [190].

CILIARY NEUROTROPHIC FACTOR-CNTF

CNTF, originally identified as a survival-promoting activity for ciliary ganglion neurons in chick eye tissue [191], is the main member of neurokine family showing neurotrophic activity across a broad spectrum of peripheral and CNS cells, including parasympathetic, sensory, sympathetic, motor, cerebellar, hippocampal and septal neurons. It is synthesized by astrocytes and acts as an autocrine and paracrine signal of astrocytic activation and hypertrophy in response to injury to CNS. In the periphery, CNTF is synthesized in muscle, released by motor neuron terminals and then retrogradely transported to cell bodies. The magnitude of transport is then increased by nerve lesion [192]. Of particular interest is the fact that CNTF partially prevents the atrophy of skeletal muscle following the formation of nerve lesions but has no effect on innervated muscle, suggesting that CNTF is primarily operative in the pathological state [193-194]. CNTF, structurally similar to the interleukin-6 family of hematopoietic cytokines, signals using common cytokine receptor components [195]. CNTF binds to the GPI-anchored alpha subunit of the CNTF receptor complex (CNTFRα) which induces the recruitment of two transmembrane receptor proteins gp130 and LIFRβ, resulting in tyrosine phosphorylation and the downstream activation of the Janus kinase/ signal transducer and activator of trancription (JAK/STAT) signalling pathway [196-197]. STAT proteins then translocate to the nucleus where they bind specific DNA sequences resulting in the transcription of responsive genes.

Since CNTF protein is mainly expressed in glial cells of peripheral nerve system and in CNS, it has been involved in several cerebral processes, such as cells fate determination of neural stem cells and neuronal and glial differentiation and development [196]. Concerning this action, the existence of a crosstalk between NTFs has been reported. In particular, CNTF and BDNF showed synergistic effects on the development and survival of multiple populations of neurons [197]; as example, CNTF was able to potentiate BDNF-induced cell survival of BFCN when added concomitantly [198]. Furthermore, CNTF has been implicated in the regulation of post-injury processes, since its levels strongly increased after injury in both peripheral and central neurons [196]. Noteworthy, recent data suggest a link among CNTF, neurogenesis and dopamine, based on the observation that CNTF enhances forebrain neurogenesis in adult mice and is expressed in astrocytes in the subventricular zone, a brain area where dopaminergic nigrostriatal projections regulate neural precursor cell proliferation [199]. This link has been reinforced by a series of *in vivo* and *in vitro* experiments that implicate CNTF as an endogenous regulatory component of dopamine D_2-receptor-dependent neurogenesis in the subventricular zone and the dentate gyrus of the hippocampus [200]. Since an imbalance in dopaminergic signalling is a pathological hallmark of several neurological diseases, such as PD, HD and ALS, and CNTF supported survival of neurons both *in vivo* and *in vitro* models of neurodegeneration [196], pharmacologically modulating CNTF may be proposed as an attractive therapeutic strategy for normalizing dopaminergic and neurogenic deficits. However, previous attempts to use CNTF as a therapeutic agent in a variety of therapeutic areas yielded disappointing results. As example, Axokine, a modified version of human CNTF with a 15 amino acid truncation of the C-terminus and two amino acid substitutions, which make it three to five times more potent and stable than CNTF in *in vitro* and *in vivo* assays, was tested in the 1990s as a treatment for ALS. Systemic delivery of recombinant CNTF failed to achieve sufficient concentrations in the brain, leading to poor efficacy, while producing adverse effects, such as weight loss. Although initially discouraging, to date, CNTF has shown some recent promise in early-stage clinical trials for HD and neurodegenerative retinal diseases [201-204] (see Table **2**).

NON-NEURONAL GROWTH FACTORS

Several NTFs have been recognized to be expressed by non neuronal cells. Non-neuronal growth factors are expressed in large concentration in the nervous system and include acidic fibroblast growth factor (aFGF or FGF-1), basic fibroblast growth factor (bFGF or FGF-2), epidermal growth factor (EGF) and insulin-like growth factors (IGFs). Concerning its potential in human clinical trials for treatment of ALS, we will focus on IGF-1, whose role as trophic and survival factor for nervous system has been reported.

INSULIN-LIKE GROWTH FACTOR-1-IGF-1

IGF-1 is a member of IGFs, a family of peptides with high sequence similarity to insulin, playing important roles in mammalian growth and development [205]. IGF-1 is predominantly formed in the liver after stimulation by circulating growth hormone (GH) and released by the pituitary gland; it is also synthesized in low concentrations in most peripheral tissues, including bone, cartilage and skeletal muscle. In the nervous system, IGF-1 and its receptors are expressed specifically in the substantia nigra [206], both in glial cells and in neurons [207]. IGF-1 was initially described as a growth mediating factor regulated in the context of the somatotrophic axis, acting through both autocrine and paracrine mechanisms in order to stimulate cell growth and differentiation of peripheral tissues and contributing to normal somatic growth [208]. IGF-1 has also acute insulin-like metabolic effects [209], increases glucose and amino acid uptake, stimulates mRNA and protein synthesis in cells and, as insulin, prevents apoptosis [210]. Noteworthy, during the last decade, IGF-1 has gained particular atten-

tion also for its role in the regulation of lifespan and brain functions [211]. IGF-1 mediates its effects by binding the extracellular α-subunits of the receptor IGF-1R and triggers a conformational change in the β-subunit, resulting in its trans-autophosphorylation in multiple tyrosine residues. This event allows recognition and further tyrosine phosphorylation of phosphotyrosine-binding domains of adaptor proteins (for a review see [212]), that transduce signal to multiple response downstream pathways, such as phosphatidylinositol-3-kinase, mitogen-activated protein kinase and FOXO pathways [213].

It is known that aging is characterized by a significant decline of metabolic and hormonal functions, which often facilitates the onset of severe age-associated pathologies. Recent evidence support the involvement of IGF-1 signalling in neuroprotection [214], in the control of aging and longevity [215], in ALS and in the development of late-onset forms of AD [27, 216]. In this context, data from literature show that insulin and IGF-1 have a direct effect on the metabolism and clearance of beta-amyloid and also influence the development of neurofibrillary tangles, the known hallmarks of AD brain [217-220]. Moreover, Araki and collegues recently demonstrated that IGF-1 may promote beta-amyloid production through a secretase-indipendent mechanism [221]. However, understanding whether IGF-1 has a specific crucial role in the modulation of beta-amyloid production still needs further elucidation. In addition to a direct effect of IGF-1 on AD pathology, it has also well documented neuroprotective effects [222] and promotes neurogenesis [223], development, differentiation, synapse formation and glucose utilization throughout the brain.

On this basis, IGF-1 may be candidate for a therapeutic approach. Currently some clinical studies are investigating its potential therapeutic role in aging and in patients affected by AD and mild cognitive impairment (see Table **2**). In this regard, a study with recombinant IGF-1 has been recently approved to verify its neuronal protective action in patients with AD and mild cognitive impairment [224], based on previous data that indicate that IGF-1 levels inversely correlate with cognitive impairment [225]. Concerning the potential use of IGF-1 in aging, a good promise is represented by a pyrazolinone-piperidine dipeptide derivative, capromorelin (CP-424,391), an investigational medication able to act as a GH secretagogue (Table **2**). Preliminary studies have shown the drug to directly raise IGF-1 and GH levels [226-227]. To date, the drug is being considered for its therapeutic value in aging because elderly people have much lower levels of GH and less lean muscle mass, which can lead to weakness and frailty [228]. IGF-1 analogs are also interesting optional compounds and their efficacy has been tested with promising results in a model of ischemia [229], thus highlighting IGF-1 signalling pathway as a promising therapeutic target for the treatment of neurodegenerative disorders. In particular, greater advances on the potential use of these compounds have been reported in ALS. Mecasermin (myotrophin), an analogue of the IGF-1, had been shown to promote neurite outgrowth in culture and to be upregulated in the spinal cord of patients with ALS [230]. Mecasermin is at the moment in a phase III clinical trial in order to evaluate its benefit in slowing the progression of weakness in ALS, by promoting muscle re-innervation, axonal growth and regeneration. However, after a 2-year treatment period, disappointing results have been reported [231]. The failure of these clinical trials with IGF-1 analogs is mainly due to poor bioavailability and difficulties in the delivery of protein into the brain; thus alternative ways to exploit IGF-1 actions for therapy are required. AAV engineered to contain the gene for IGF-1 may be an option for a targeted delivery of IGF-1 to motor neurons, since, after intramuscolar injection, the gene vector is transported to the neuronal cell body by retrograde axonal transport along motor neurons [232]. However, human safety, dose schedule, and pharmacokinetics have not yet been established for this novel gene therapy. A small phase II trial of AAV engineered to contain the gene for IGF-1 is planned for the near future [233].

NEUROTROPHIC FACTORS AND THE CROSSTALK BETWEEN INFLAMMATION AND NEURODEGENERATION

In recent years, several functions of NTFs beyond the nervous system have been described. Several data on NTFs role on the immune system and on models of autoimmune demyelination, such as experimental autoimmune encephalomyelitis (EAE) have been reported and, in particular, we focused on the functions of some neurotrophins (NGF and BDNF) and CNTF.

NGF regulates a variety of immune functions; it is involved in proliferation, differentiation and antibody synthesis of B cells, in proliferation and expression of cytokine receptors in T cells and in chemotaxis of macrophages and neutrophils [234-236]. BDNF may play a role in the innate and adaptive immune system. This neurotrophin is expressed in primary and secondary lymphoid organs and is found in T and B cells, in monocytes [237] as well as in granulocytes, bone marrow cells [238] and mast cells [239], even if the physiological relevance of its expression in some of these cell types has not been fully elucidated yet. Furthermore, both NGF and BDNF have been found to play a role in the activation of bronchial eosinophils and the regulation of eosinophilic inflammation in allergic asthma [240-241]. Also some hints concerning an interaction between CNTF and the immune system may be made based on the observation that CNTF may promote an acute-phase response in the liver when administered peripherally [242], an adverse effect that limits its clinical application. Regarding CNTF, recent data from literature showed its ability to interact with the immune system in autoimmune demyelination [243-244]. In particular, when administered intraperitoneally, CNTF inhibited inflammation in the spinal cord, thus ameliorating the clinical course of EAE during time of treatment. In addition to CNTF, several studies also investigated the role of NGF and BDNF in autoimmune demyelination. In particular, an upregulation of NGF in glial cells during EAE and in the cerebrospinal fluid in patients affected by multiple sclerosis has been reported [245], whereas the exogenous application of human NGF delayed the onset of EAE and decreased the extent of EAE lesions [246]. Also BDNF secretion of immune cells and serum from patients with multiple sclerosis was found increased [247], even if these data were not always reproduced [248], and the application of BDNF-transduced bone marrow stem cells was able to reduce the course of EAE and inflammatory infiltration in the spinal cord [249].

As previously reported, during aging a fragile balance between NTFs support and dysfunction occurs, which may be at the base of the link between inflammation and neurodegeneration [250]. It has been postulated that the activation of the immune system is different and dependent on a discordant brain inflammatory response in aged compared with younger organisms [251]. The aging brain is characterized by a shift from the homeostatic balance of inflammatory mediators to a proinflammatory state. This increase in neuroinflammation is marked by increased numbers of activated and primed microglia, increased steady-state levels of inflammatory cytokines and decreases in anti-inflammatory molecules. These conditions sensitize the aged brain to produce an exaggerated response to the presence of an immune stimulus in the periphery or following exposure to a stressor [252]. Therefore, accumulation of proinflammatory cytokines during aging has been hypothesised to lead to a "neurotrophin resistance" state that places the brain at risk for cognitive decline and neurodegenerative diseases [253]. Within this context, strategies to overcome cellular resistance to NTFs signaling are strongly required. One attempt was made in order to counteract the accumulation of pro-inflammatory cytokines. Tumor necrosis factor alpha (TNF-α) is an immunomodulating cytokine promoting acute-phase reactions and, when chronically elevated,

can induce degenerative changes. In the context neuroinflammation/neurodegeneration, TNF-α is able to increase interleukin-1 expression, in turn involved in production of the precursors necessary for formation of hallmarks of neurodegenerative diseases, such as amyloid plaques, neurofibrillary tangles and Lewy bodies [254]. A number of reports have recently been published regarding an experimental treatment for AD by using the anti TNF-α antibody, etanercept [255-257]. In particular, the case report by Tobinick demonstrated that perispinal administration of etanercept, a large molecule unable to cross the blood brain barrier following conventional systemic administration, may provide a rapid and sustained improvement in cognitive function for six months in patients with mild, moderate and severe AD [256]. Such rapid gain of function led to speculate that this drug may be able to counteract gliotransmission or other equally rapid synaptic events in the human brain [258]. Moreover, this treatment approach utilizes therapeutic delivery of etanercept across the dura via the cerebrospinal venous system and may suggest the possibility that perispinal delivery of other biologics, such as vascular endothelial growth factor antagonists, interleukin antagonists, or NTFs, might be useful for the treatment of additional neurodegenerative disorders. However, the use of this anti TNF-α antibody to treat AD and the way these studies were conducted is still controversial and requires further investigation. Human data demonstrating that etanercept reaches either the cerebrospinal fluid or the central nervous system in sufficient concentrations to inhibit the action of TNF when administered perispinally and any placebo-controlled data are to date missing. The latter would test whether any response is due to the drug or to something else associated with the procedure. Furthermore, some criticisms also concern the reported rapidity of response which is still to be proved mechanistically when considering the time required for resolution of an active inflammatory response and the potential impact that this could have on cognition.

NEUROTROPHIC FACTORS-BASED THERAPY AND RELATED MECHANISMS

Normally, regulation of NTFs signalling is under exquisite control. However, the presence of an altered availability of NTFs or one of their dependent kinases may affect the regulation of neuronal survival and behavior thus resulting in the onset of neurodegenerative cascades contributing to aging as well as to the pathogenesis of diseases. In the adult central nervous system affected by age or disease-related degeneration, mechanisms of compensation and repair are activated in an attempt to counteract functional sequelae of neuronal loss [259-260]. As a consequence, degenerative events become manifest as a disorder only after exceeding a critical threshold, thereby exhausting the capacity of compensation [261]. However, it is worth to highlight that, under certain conditions, these compensational processes might be maladaptive and eventually even contribute to the development and progression of the disease. This seems to be the situation in AD, where an aberrant dendritic growth is observed instead of the regular dendritic growth seen during aging and in a variety of related degenerative disorders [262-263].

When considering NTFs network, one attempt is represented by compensating the missing component. However, it is worth to underline that in a biological network the altered availability of a component leads in turn to modify its cellular interplay. In fact, regulatory mechanisms are activated. As an example, several biological mechanisms may take part in neural-level synaptic modifications that self-regulate neuronal activity; these include receptor up-regulation and downregulation [264], activity-dependent regulation of membranal ion channels [265], and activity-dependent structural changes that reversibly enhance or suppress neuritic outgrowth [266]. These observations in turn suggest that in a system with altered ratios the simple substitution theraphy is not appropriate and this may in part explain why NTFs integration alone to prevent aging and treat neurodegenerative disorders is to date not totally effective. To better clarify, as an example, the model of stroke can be considered, where an increased knowledge of the complex pathophysiology has been reached due to the great availability of animal models [267]. In stroke, a neuroprotective intervention points at inhibiting a cascade of pathological molecular events occurring under ischaemia and resulting in calcium influx, activation of free radical reactions and cell death. To date, in human stroke trials, the use of a single agent has been unable to prove a clinically valuable effect, because treatment has often been initiated much later than in successful experimental stroke models, and because of insufficient doses or low availability of the drug at the target area. Hence, as future new approach, a combination of neuroprotective agents should be strongly proposed to address several of the compromised mechanisms [268].

CONCLUSIONS/PERSPECTIVES

Restricted availability of NTFs is critical in the developmental regulation of neuronal survival and behavior and can set the stage for neurodegenerative cascades contributing to aging as well as to the pathogenesis of diseases. To date a question is still debated: Is there a future for NTFs in preventing aging and in the treatment of neurodegenerative diseases? The simple answer based on data here presented, in particular on gene-therapy and NTFs mimetics, would be "no", but this seems premature in view of the fact that the research is still in its infancy. The ability to promote endogenous repair through the use of targeted growth factor delivery is an attractive approach. In addition, the development of small molecules that specifically activate NTFs receptor and can be administered systemically could represent a valid option, since it would overcome most of the problems associated with the delivery of NTFs into the brain, with their expression induced by viral vectors, or with the use of encapsulated growth factors producing cells. Although animal and human studies provide hope for the therapeutic application of NTFs or mimetic molecules, they also indicate that further studies are needed to optimize therapeutic effects and minimize adverse effects. As with all pharmacological manipulations, it is known that an excess neurotrophic stimulation (or an improper localization of the stimulation) can result in deleterious adverse effects. For example, patients reported pain at NGF injection sites, putatively as the result of abnormal local nerve sprouting [269]. Side effects may also result from the fact that growth factors can also affect non-neuronal cells. NGF administration induces Schwann cells hyperplasia *in vivo* [270]. BDNF stimulates oligodendrocyte proliferation during axonal regeneration [271], whereas NGF kills cultured mature oligodendrocytes via a p75-mediated mechanism [272]. Furthermore, cardiovascular side effects or angiogenesis [273] could occur after NTFs systemic application, since they also play a role in the development and maintenance of large blood vessels [274]. Finally, growth factors can also promote the survival, proliferation and metastasis of many tumor subtypes. These potential disadvantages to the development of molecules that promote neurotrophic function suggest that ideal compounds would work in synergy with existing NTF molecules and enhance rather than directly stimulate neurotrophic activity.

In addition, another point has to be considered, namely that therapeutic benefit may be dependent on the extent of neurodegeneration before therapy initiation. Thus, within this context, although studies will be difficult, assessment of the effects of NTFs on the rate of progression over longer time frames could probably be critical in determining their ultimate efficacy.

Therefore, while critically reflecting on the new trials result, much has still to be learnt about the useful application of NTFs and to abandon it at this stage could be premature.

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ABBREVIATIONS

AAV	=	Adeno-Associated Virus
AChE	=	Acetylcholinesterase
AD	=	Alzheimer's disease
aFGF	=	Acidic Fibroblast Growth Factor
ALS	=	Amyotrophic Lateral Sclerosis
ART	=	Artemin
BDNF	=	Brain-Derived Neurotrophic Factor
BFCN	=	Basal Forebrain Cholinergic Neurons
bFGF	=	Basic Fibroblast Growth Factor
ChAT	=	Cholinoacetyltransferase
CNTF	=	Ciliary Neurotrophic Factor
EAE	=	Experimental Autoimmune Encephalomyelitis
EGF	=	Epidermal Growth Factor
GDNF	=	Glial-cell-line-Derived Neurotrophic Factor
GFR	=	GDNF Family Receptors
GH	=	Growth Hormone
GPI	=	Glycosyl Phosphatidylinositol
HD	=	Huntington's disease
5-HT	=	Serotonin
IGF-I	=	Insulin-like Growth Factors I
IGFs	=	Insulin-like Growth Factors
LIF	=	Leukemia Inhibitory Factor
LIFR	=	Leukemia Inhibitory Factor Receptor
LTP	=	Long-Term Potentiation
MPTP	=	1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine
NGF	=	Nerve Growth Factor
NRTN	=	Neurturin
NT-3	=	Neurotrophin-3
NTFs	=	Neurotrophic Factors
PD	=	Parkinson's disease
TGF	=	Transforming Growth Factor
TNF	=	Tumor Necrosis Factor
Trk	=	Tyrosine Receptor Kinase

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